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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,664	02/18/2004	Felix A. Montero-Julian	2512.0210001/KWM(2052-183	5199

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STERNE KESSLER GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
11/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,664	MONTERO-JULIAN ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9,11,13-16,20-22,25,27-34,36,38-41,45-50 and 74-87* is/are pending in the application.

4a) Of the above claim(s) *7,8,15,16,23,24,32,33,39-41,48,49 and 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6,9,11,13,14,20-22,25,27-31,34,36,38,45-47,50,74-77 and 79-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/09*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 6/25/09 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I, and species of HLA-A2/β2m/MART-1 as the MHC/template peptide complex in Applicant's responses filed 3/27/07 and 11/13/06. In addition, Applicant is reminded of Applicant's election of the species 100x molar excess of competitor peptide, incubating the sample for about 2-20 hours at about 21 degrees C, HBc 18-27 tagged with FITC as the tracer peptide, only one competitor peptide is used and soluble HLA molecule in Applicant's response filed 3/27/07.

Claims 2-6, 9, 11, 13, 14, 20-22, 25, 27-31, 34, 36, 38, 45-47, 50, 74-77 and 79-87 are currently being examined.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 74 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 recites the limitation "system" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Base claim 87 recites "kit".

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record on page 11-12 of the amendment filed 6/25/09, briefly that the claim has been amended to delete the limitation "system" and to recite "kit." However, one instance of "system" has not been so deleted.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 2-6, 9, 11, 20-22, 25, 27-31, 34, 36, 45-47, 50, 79, 81, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07952 A1 (IDS reference filed 7/12/07) in view of US 2003/0191286 A1 (of record).

Claims 2-6, 9, 11, 20-22, 25-31, 34, 36, 45-47, 50, 79 and 81 were rejected in the prior Office Action of record upon the basis set forth below. Applicant's amendment filed 6/25/09 has necessitated the inclusion of newly added claims 85 and 86 in this rejection.

WO 92/07952 A1 teaches determining the binding affinity of a candidate peptide for a specific MHC molecule (*i.e.,* MHC heavy chain and β2m) using competition between detectable agonist peptide (a peptide known to bind to MHC that may or may not be labeled with fluorophore) (claims 6 and 31) such as fluoresce in (FITC) (claims 9 and 34) and the candidate peptide (*i.e.,* a peptide that is a competitor peptide) in up to 100-fold more from the agonist peptide. WO 92/07952 A1 teaches testing one or more concentration of candidate peptide on binding of the agonist peptide. WO 92/07952 A1 teaches an incubation time between about 12 and 48 hours at, for example, 37 degrees C (*i.e.,* "about 21 degrees C) (pages 8-9 at line 32, paragraph spanning pages 7-8). WO 92/07952 A1 teaches preloading an isolated MHC glycoprotein with a homogeneous peptide preparation, the peptide chosen to be comparatively readily released by the MHC molecule (especially page 13 at lines 19-35, page 14 at lines 1-23, page 4 at the last paragraph, and claims). WO 92/07952 A1 teaches separating the bound agonist from the unbound agonist and detecting the amount of agonist bound in the complex as a function of the concentration of test compound in the reaction mixture, including coupling the agonist peptide to biotin and separating by means of coupling the complex to a solid support via linkage with streptavidin (see entire reference, especially claims).

WO 92/07952 A1 does not teach that the MHC molecule is HLA-A2.

US 2003/0191286 A1 discloses making soluble MHC class I molecules, including HLA-A2, with or without endogenous peptides loaded therein, and further discloses representative HLA-A2 binding peptides of nine or ten amino acid residues in length (see entire reference, especially [0157], [0032], [0190] and claims). US 2003/0191286 A1 further discloses at [0085] "Cloned genomic DNA fragments contain both exons and introns as well as other non-translated regions at the 5' and 3' termini of the gene. Following transfection into a cell line which transcribes the genomic DNA (gDNA) into RNA, cloned genomic DNA results in a protein product thereby removing introns and splicing the RNA to form messenger RNA (mRNA), which is then translated into an MHC protein. Transfection of MHC molecules encoded by gDNA therefore facilitates re-isolation of the gDNA, mRNA/cDNA, and protein. Production of MHC molecules in non-mammalian cell lines such as insect and bacterial cells requires cDNA clones, as these lower cell types do not have the ability to splice introns out of RNA transcribed from a

gDNA clone. In these instances the mammalian gDNA transfectants of the present invention provide a valuable source of RNA which can be reverse transcribed to form MHC cDNA. The cDNA can then be cloned, transferred into cells, and then translated into protein. In addition to producing secreted MHC, such gDNA transfectants therefore provide a ready source of mRNA, and therefore cDNA clones, which can then be transfected into non-mammalian cells for production of MHC. Thus, the present invention which starts with MHC genomic DNA clones allows for the production of MHC in cells from various species."

It would have been prima facie obvious to one of ordinary skill in the art to have used the soluble HLA-A2 monomers disclosed by US 2003/0191286 A1 as the MHC molecule in the method taught by WO 92/07952 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 92/07952 A1 teaches a method of determining binding affinity of a candidate peptide for a specific MHC molecule, and US 2003/0191286 A1 discloses that HLA-A2 is a specific MHC molecule and further discloses methods to make soluble MHC molecules.

Although the art reference does not explicitly teach "wherein the template peptide has lower or intermediate affinity as compared with the tracer peptide for the monomer," the art reference teaches there is peptide exchange and measurement of radioactively labeled tracer peptide and also teaches that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

With regard to the limitation recited in instant claims 4 and 29 "wherein said liquid phase condition includes incubating the sample for about 2 to 20 hours," the art reference teaches incubating 2 days or 48 hours, and so meets the claim limitation.

With regard to the limitation recited in instant claims 5 and 30, "wherein said liquid phase condition further includes incubating the sample at about 21 degrees C," the art reference teaches incubating at room temperature or 37 degrees C, and so meets the claim limitation.

Claims 2-6, 9, 11, 20-22 and 25 are included in this rejection because the art method of measuring affinity of a peptide of interest is also identifying said peptide for binding to MHC.

With regard to the recited limitation in instant claims 3 and 28, the said limitation is not a test step. Although the art reference does not explicitly teach "wherein the tracer peptide displaces at least 90% of the template peptide in a parallel competition assay conducted in the absence of the first competitor peptide," the art reference teaches there is peptide exchange and measurement of radioactively labeled tracer peptide and also teaches that the preloaded peptide is preferably chosen to be comparatively readily released by the MHC molecule. Therefore, the claimed method appears to be similar to the method of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the method of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's arguments are of record in the amendment filed 6/25/09 on pages 12-20.

Applicant first makes the general argument that the cited references fail to teach or suggest the claimed methods and provide no apparent reason to combine the references cited by the Examiner to arrive at the claimed invention and that a person of ordinary skill in the art would have no reasonable expectation of success in making the claimed invention.

However, motivation to combine the references is found in the teachings of the references, *i.e.*, that the primary reference teaches an assay that utilizes MHC molecules and the secondary reference teaches a commonly expressed MHC molecule.

Applicant makes a specific argument that the primary reference teaches that the agonists will be at a concentration of about 0.1-50 times the concentration of the MHC glycoprotein and references page 9 at lines 3-5 for the said teaching. Applicant asserts that in view of this large concentration range of the agonist peptide (*i.e.*, the tracer peptide), it would not have been obvious to a person of skill in the art which method to apply to create "conditions where the agonist is known to form a complex with the MHC glycoprotein," the latter referring to one of two ways in which the Applicant asserts the agonist may displace an endogenous peptide to form a complex with the MHC (1) The affinity for the monomer of the agonist is higher than those of the endogenous peptides, and (2) When the agonist is present in a molar excess so as to displace the endogenous peptides, irrespective of their relative binding affinities to the MHC).

However, endogenous peptides (*i.e.*, hundreds of different peptides) are not involved in the assay taught by the primary reference, but rather a preloaded homogenous peptide is, and thus it would have been well within the purview of one of ordinary skill in the art

at the time the invention was made to have determined the appropriate conditions for displacing the preloaded peptide.

Applicant further argues that the method taught by the primary reference involves dilution of the preloaded MHC complexes to dissociate the homogenous peptide agonist from the MHC complex prior to incubating with the oncoming agonist (*i.e.,* the tracer peptide) and the candidate moiety (*i.e.,* the competitor peptide), creating an empty MHC molecule, in contrast to the method recited in the instant claims.

However, although the primary reference teaches an assay that provides empty MHC molecules by pre-diluting the preloaded MHC complexes, it also clearly teaches an assay that provides MHC molecules preloaded with a homogenous peptide and not pre-diluted (see for example, the primary reference WO 92/07952 A1, Rothbard *et al*) at page 4, last paragraph and claim 15). Thus, Applicant's argument as to this point is moot.

Applicant asserts that the primary reference teaches the homogenous preloaded peptide is preferably chosen to be comparatively readily released by the MHC glycoprotein, and that this statement is made in the context of the peptide being easy to dislodge from the MHC monomer upon dilution of the monomer. Applicant argues that no mention is made in the said reference regarding the comparison of the binding affinity of the homogenous preloaded template peptide for the MHC monomer *vis-à-vis* that of the tracer peptide.

However, the primary reference teaches in claim 15 of the said reference that the second agonist (*i.e.,* the tracer peptide) competes for binding to the MHC, a non-explicit teaching of higher affinity of the tracer peptide as compared to the preloaded template peptide for the MHC.

Applicant argues that the primary reference does not teach a concentration of competitor peptide which is about or more than 100-fold molar excess compared to the tracer peptide and references page 9 at lines 18-20.

However, first as a side point, the instant claims recite "an excess amount of a first competitor peptide" and does not recite that the excess amount refers to comparison with the tracer peptide. Second, the teaching on page 9 at lines 18-20 is that "Usually, the amount of the candidate will not differ by more than about 100-fold from the amount of the agonist (*i.e.,* the tracer peptide) present in the medium." Instant claims 2 and 27 recite "wherein the excess amount of the first competitor peptide is about or more than 100-fold molar excess." Thus, the art teaching 'about 100-fold molar excess' meets the said claim limitation.

Applicant also argues that the instant invention claims a method of detection of the bound peptide by determining a difference in signal produced by the detectable label in the total sample as compared with signal produced solely by [the] monomer obtained from the sample after incubation, wherein the difference indicates affinity of the first competitor peptide for the monomer. Applicant asserts that the primary reference teaches determination of the labeled tracer peptide bound to the MHC molecules as a function of the concentration of the competitor peptide in the reaction mixture, and thus does not disclose or suggest determining a difference in signal in the total sample as compared with the signal produced solely by the isolated monomer in the presence [or] absence of the competitor peptide as claimed in the instant application.

However, the art method encompasses 'determining a difference in signal produced by the detectable label in the sample as compared with [the] signal produced solely by [the] monomer obtained from the sample after the incubation' because the second agonist (*i.e.*, the tracer peptide that is labeled) is what is measured.

Applicant argues the secondary reference separately.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant asserts that because it would not have been possible for a person of skill in the art to reconstitute the present invention from the teachings of the primary reference, either alone or in view of the secondary reference, a person of skill in the art would not have looked to combine disparate portions of the primary reference to reconstruct the instant invention and the rejection thus constitutes improper hindsight analysis.

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

One of ordinary skill in the art would have been motivated to make the claimed invention given the teachings of the combined references, and with a reasonable expectation of success, in order to perform the assay taught in the primary reference with an MHC class I molecule as taught by the primary reference, using an MHC class I molecule from humans, HLA-A2, that is disclosed by the secondary reference, for the reasons of record and those enunciated herein supra.

7. Claims 13, 14, 38, 74-77, 80, 82-84 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07952 A1 (IDS reference filed 7/12/07) in view of US 2003/0191286 A1 (of record) as applied to claims 2-6, 9, 11, 20-22, 25, 27-31, 34, 36, 45-47, 50, 79, 81, 85 and 86 above, and further in view of Mitchell *et al* (Cancer Research 2000, 60: 6448-6456), US 2004/0214995A1 and US 2002/0106708 A1 (IDS reference filed 6/26/08).

Claims 13, 14, 38, 74-77, 80 and 82-84 were previously rejected in the prior Office Action of record upon the basis set forth below. Applicant's amendment filed 6/25/09 has necessitated the inclusion of newly added claims 85-87 in this rejection.

The combination of WO 92/07952 A1 and US 2003/0191286 A1 has been discussed above, hereafter referred to as "the combined references."

The combined references do not teach wherein the monomer is HLA-A2/MART-1_{26-35} (claims 13 and 38), nor wherein the tracer peptide is HBc 18-27 (claim 14), nor wherein the HLA-A2 monomer is that produced in *E. coli* (claims 80, 82 and 84), nor wherein the ternary complex comprising the HLA-A2 monomer with template MHC-binding peptide and the tracer peptide tagged with a detectable label are comprised in a kit for identifying an MHC binding peptide for the HLA-A2 monomer (claims 74-77, 83, 84 and 87), nor wherein the kit further comprises an instruction for using the kit (claim 74).

Mitchell *et al* teaches use of the HBc 18-27 peptide labeled with a detectable label and competing unlabeled putative epitope peptides for binding to HLA-A2.

US 2004/0214995A1 discloses the low affinity peptide MART-1_{26-35} that binds to HLA-A2 ([0224]), and also discloses the production of proteins in *E. coli*. US 2002/0106708 A1 discloses placing components of assays into kits (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MART-1_{26-35} peptide as the template MHC binding peptide bound to HLA-A2 in the method taught by the combined references, to have used an HLA-A2 monomer that was produced in *E. coli*, and to have placed the components of the assay (*i.e.*, the monomer with template binding peptide bound thereto and a tracer MHC-binding peptide tagged with a detectable label) in a kit, including with instructions for use.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 92/07952 A1 of the combined references teaches preloading an isolated MHC glycoprotein with a homogeneous peptide preparation, the peptide chosen to be comparatively readily released by the MHC molecule, and US 2004/0214995A1 discloses that the peptide MART-1_{26-35} exhibits low affinity binding to HLA-A2, while Mitchell *et al* teaches use of the HBc 18-27 peptide labeled with a

detectable label as a tracer peptide. One of ordinary skill in the art at the time the invention was made would have been motivated to have used HLA-A2 that was produced in *E. coli* because US 2003/0191286 A1 discloses making HLA-A2 in bacterial cells and US 2004/0214995A1 discloses that recombinant proteins may be produced in *E. coli*. One of ordinary skill in the art at the time the invention was made would have been motivated to have placed the components of the assay in a kit for convenience sake.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment filed 6/25/09 on pages 20-22.

The Examiner's comments regarding Applicant's arguments set forth at item #6 supra, apply herein.

8. No claim is allowed.

9. With regard to Applicant's Form 1449 filed 10/2/09: The references listed as "FP18 and "FP19" have been crossed out by the Examiner because they are not in the English language and no concise explanation of relevance has been provided by Applicant (see MPEP 609 [R-7] and 37 CFR 1.98(3)(i)). The reference listed as "NPL57" has been crossed out because it is not a complete citation.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
November 2, 2009

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1644